REMARKS

Claims 1-109 were pending. Claims 1, 9, 23, 41 and 81-90 have been amended for clarity and to highlight certain aspects of the invention. Applicants submit that these amendments are fully supported by the specification. Support for the amendments to claims 1, 23, and 81-90 may be found at page 12, lines 15-17; support for the amendments to claim 9 may be found at page 14, lines 1-14, and page 30, lines 9-30. Applicants have also provided a Substitute Specification to amend the priority paragraph, to correct typographical errors, to insert the trademark identifiers ™ or ® and generic terminology, and to insert sequence identifiers where necessary. No new matter has been introduced.

The Examiner has withdrawn claims 2-8, 22, 24-29, 33-37, 39, 40, 44-80, and 91-103 from further consideration under 37 C.F.R. § 1.142(b) as drawn to a non-elected invention.

Objections to the Application and/or Specification under 37 C.F.R. §§ 1.821-1.825 and Response to Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures

The Examiner has objected to the application for failing to comply with requirements of 37 C.F.R. §§ 1.821-1.825. In particular, the Examiner points to the objections outlined in the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures ("Notice"). The Notice, a return copy of which is submitted herewith, identifies that the application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. § 1.821(c), and that a copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. 0.821(e). In response, Applicants submit herewith a Sequence Listing in paper and computer readable form pursuant to 37 C.F.R. §§ 1.821 (c) and (e). Applicants additionally submit herewith a Transmittal of Sequence Listing, which states that the paper and computer readable forms of the Sequence Listing are the same and include no new matter, pursuant to 37 C.F.R. 1.821 §§ (e), (f) and (g).

The Examiner has objected to the specification for failing to comply with sequence rule 37 C.F.R. § 1.821, in particular, for failing to reference the amino acid sequence on page 12 of the instant specification with an assigned identifier. Applicants presume that the Examiner is referring to the amino acid sequence SDPNSFI, recited at page 12, line 34 of the instant specification. In response, Applicants have amended the specification at page 12 to identify the sequence with an appropriate sequence identifier. Applicants have further amended the specification at page 50, Table 2, to identify the sequences in the table with appropriate sequence

identifiers. Applicants submit herewith a Sequence Listing as discussed above, which includes the added sequence identifiers. Applicants have also requested hereinabove that the paper Sequence Listing submitted herewith be entered into the Specification.

In view of the foregoing, Applicants submit that the objections to the specification and/or application for failing to comply with 37 C.F.R. §§ 1.821-1.825 have been obviated and request that the objections be withdrawn.

Objections to the Specification

The Examiner has required that the specification be reviewed for spelling, for the use of Trademarks and, where necessary, amended such that the Trademarks are indicated appropriately. The Examiner has also required that the specification at page 1, line 1 (the "priority" paragraph) be amended to include a specific reference to priority application PCT/US03/25399 for which benefit is sought. In response, as indicated hereinabove, Applicants provide herewith a Substitute Specification in marked-up and clean form that amends the specification as filed to correct typographical errors, to insert Trademark identifiers and/or generic terminology and to correct the priority statement.

The Rejections Under 35 U.S.C. § 112, Second Paragraph, For Indefiniteness, Should Be Withdrawn

The Examiner has rejected claims 9, 12, 31, 41 and 109 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the invention.

The Examiner contends that claims 9 and 14 are indefinite for recitation of the phrases "at least one activity of FcγRIIB" and "B cell activity," respectively, because allegedly it is unclear as to which activities or requisite structural/functional characteristics are intended or encompassed by the claimed antibody. Preliminarily, Applicants respectfully submit that recitation of claim 14 in this objection (see paragraph 7A at page 4 of the Office Action) is in error because claim 14 does not recite the phrase "B cell activity." Applicants believe that the rejection is to claim 12, which was listed in the claims rejected under 35 U.S.C. § 112 (see paragraph 7 at page 4 of the Office Action), and which recites the phrase "B cell activity."

In response, Applicants have amended claim 9 to recite that the at least one FcγRIIB activity is selected from the group consisting of activation of B cell receptor-mediated signaling and activation of FcεRI-induced mast cell activation. Applicants submit that the amendment clearly conveys to one of skill in the art the meaning of the term "FcγRIIB activity" in the context of the claim, thus obviating the objection.

With respect to the rejection of claim 12, Applicants respectfully disagree with the Examiner for the following reasons. Applicants submit that the term "B cell activity" is well understood in the art. Words in the claims are generally given their ordinary and customary meaning, as understood by one of ordinary skill in the art at the time of the invention. See Phillips v. AWH Corp., 415 F.3d 1303, 1312-13; Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). The study of immune system function, and in particular B cell function, is not a novel endeavor and the literature is rife with teachings B cell function and/or activity. As such, one of skill in the art could readily ascertain the meaning of the term "B cell activity" in the context of these claims.

The Examiner has further rejected claim 31 under 35 U.S.C. § 112, second paragraph for recitation of the phrase "immune response" wherein allegedly it is unclear as to which "immune response" or to which requisite structural/functional characteristics are intended or encompassed by the claimed antibody. Applicants respectfully disagree with the Examiner's rejection for the reasons outlined below.

Applicants submit that one skilled in the art would readily understand the phrase "immune response" as used in the context of the claim 31. Claim 31, as dependent on claim 30, is drawn to an antibody of the invention that blocks the binding Ig-Fc to FcγRIIB and that enhances an immune response. As was known in the art at the time of filing, and as is described in the specification, the FcγRIIB receptor is associated with inhibitory signaling in immune cells in which it is expressed, *e.g.*, B cells, resulting in a dampening of "the activating response ... and inhibit[ing] cellular responsiveness .... B cell activation, B cell proliferation and antibody secretion [are] thus aborted" (see Specification at page 2, lines 25-34 and page 3, lines 7-17). It would thus be clear to one of skill in the art that an antibody of the invention that blocks binding of Ig-Fc to FcγRIIB also blocks inhibitory signals mediated through FcγRIIB signaling, enhancing the cellular response, *e.g.*, to an antigen, such as in the context of a vaccine (see the specification at page 109, lines 6-9), relative to the condition wherein the antibody of the invention is not present. As such, one of skill in the art could readily ascertain the meaning of the term "immune response" in the context of these claims. Thus, Applicants submit that the "immune response" in the context of claim 31 is not ambiguous and respectfully request that the rejection of claim 31 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Examiner has rejected claim 41 under 35 U.S.C. § 112, second paragraph, for recitation of the term "humanized," wherein there is allegedly no antecedent basis for the term "humanized." In response, applicants have amended claim 41 to recite, "[a] humanized version of the antibody of claim 38," thus obviating the rejection.

The Examiner has rejected claim 109 under 35 U.S.C. §112, second paragraph, as indefinite for recitation of the phrase "denatured," wherein the phrase is allegedly undefined by the claims and the specification allegedly does not provide a standard for ascertaining the requisite degree, presumably of "denatured." Applicants respectfully disagree with the Examiner's position, and submit that the term "denatured" is well understood in the art, in particular in connection with the binding of an antibody to a "denatured" protein as recited in claim 109. Assays to determine the binding of an antibody to an antigen are routine, in particular with respect to the binding of a antibody to a protein subsequent to SDS-PAGE, *i.e.*, a Western blot. Considering the routine nature of such assays, it would thus be clear to one of skill in the art that a "denatured" protein, *i.e.*, denatured FcγRIIB, as recited in claim 109 refers to a protein that has been "denatured" by SDS-PAGE or similar electrophoresis separation assay. In view of the foregoing, Applicants submit that the rejection has been obviated or overcome and request that the rejection of claim 109 under 35 U.S.C §112, second paragraph, be withdrawn.

Accordingly, in view of the foregoing, the rejections under 35 U.S.C. § 112, second paragraph, have been overcome or obviated and should be withdrawn.

The Rejection Under 35 U.S.C. §112, First Paragraph, For Lack of Enablement, Should Be Withdrawn

Claims 38 and 41-43 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly not containing subject matter which was described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For the reasons detailed below, the rejections under 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand and should be withdrawn.

Availability of ATCC Deposit

The Examiner contends that an affidavit or declaration by Applicants, or a statement by an attorney of record is required to assure that the deposited material recited in claims 38 and 41-43 will be irrevocably and without restriction released to the public upon the issuance of a patent (see Office Action at page 6, paragraph 9). Applicants respectfully direct the Examiner's attention to the attached Statement of Attorneys for Applicants Regarding the Permanence and Availability of Deposited Microorganisms ("Statement"; Exhibit A), which attests to the deposit of microorganisms according to the provisions of the Budapest Treaty, in compliance with the criteria set forth by 37 C.F.R. §§ 1.801-1.809 regarding the availability and permanence of deposits. Accordingly, the Statement obviates the Examiner's rejection based on the availability

of the deposited material recited in new claims 111, 115, 119, 123, 143, 144, 145, and 154, and dependent claims thereon.

The Rejection Under 35 U.S.C. § 102(a) Should Be Withdrawn

The Rejection Under Weinrich

The Examiner has rejected claims 1, 9-16, 23, 30-32, 81-90, 108 and 109 under 35 U.S.C. § 102(a) as anticipated by Weinrich et al., 1996, Hybridoma 15:109-116 ("Weinrich") as evidenced by Bolland et al., 1999, Adv. Immunol. 72:149-177 ("Bolland") and Clynes et al., 2000, Nature Med. 6:443-446 ("Clynes"). Applicants submit that the rejection under Weinrich as evidenced by Bolland and Clynes is in error for the reasons set forth below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.,* 52 F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F.2d. 1565, 1576 (Fed. Cir. 1991).

As amended herein, each embodiment of the invention as claimed in independent claims 1, 23 and 81-90 (and therefore all remaining pending claims, which are dependent thereon) recites, in part, that the isolated antibody or fragment thereof comprises a variable domain that specifically binds to FcγRIIB endogenously expressed on the surface of a cell. In contrast, Weinrich discloses the production of a monoclonal antibody, II8D2, that is used in Western blot, immunoblot, or immune precipitation procedures. Accordingly, Weinrich does not demonstrate that II8D2 binds FcγRIIB that is endogenously expressed on the surface of a cell.

Moreover, additional evidence shows that II8D2 does not in fact bind FcγRIIB that is endogenously expressed on the surface of a cell. The Examiner's attention is respectfully invited to Exhibit B, Budde et al., 1995, "Specificity of CD32 mAb for FcγRIIa, FcγRIIb1, and FcγRIIb2 expressed in transfected mouse B cells and BHK-21 cells, in Leucocyte Typing V, White Cell Differentiation Antigens, Vol. I, (eds. Schlossman et al.), 828-832, previously submitted as reference **C09** in the July 15 IDS ("Budde"). Budde, published by many of the same authors as Weinrich, discloses that antibody II8D2 is only reactive with *recombinantly* expressed FcγR in BHK-21 cells and that, notably, the antibody fails to bind Daudi cells (see Budde, Table I, page 829), which endogenously express FcγRIIB (see Budde, 828, first column, line 7). Budde also shows that II8D2 does not bind either FcγRIIa or FcγRIIb recombinantly expressed in IIA1.6

cells. Accordingly, Weinrich does not disclose an antibody or fragment thereof comprising a variable domain that specifically binds to FcγRIIB endogenously expressed on the surface of a cell, and thus does not teach each and every element of claims 1, 23 and 81-90. Therefore, Weinrich cannot anticipate these claims. Because Weinrich does not anticipate any of claims 1, 23 and 89-90, the reference also does not anticipate remaining claims 9-16, 30-32 and 108-109 dependent from these claims.

Applicants also point out that Budde reports another antibody, KB61, that shows apparently greater reactivity with IIA1.6 cells that recombinantly express FcγRIIb1 or FcγRIIb2 than with IIA1.6 cells that recombinantly express FcγRIIaLR or FcγRIIaHR (see Budde, Table 1, page 829). However, applicants note that Budde provides no controls for this experiment (such as normalizing based on the level of expression of the recombinant protein and/or demonstrating a lack of binding in non-transfected cells), or any discussion thereof, providing no basis for comparison of the antibody's reactivity among independently transfected cell lines. In addition, Budde reports that KB61 exhibits similar reactivity to FcγRIIa and FcγRIIb expressed in BHK-21 cells and similar reactivity to both Daudi and K-562 cells, which endogenously express FcγRIIB and FcγRIIa, respectively. In view of the lack of controls for the level of receptor expression and conflicting results, one cannot determine the binding specificity of KB61 from the results presented in Budde.

Applicants have, however, investigated the binding specificity of KB61. The binding of KB61 to soluble extracellular domains of FcγRIIA and FcγRIIB was assessed by surface plasmon resonance. Applicants' results demonstrate that KB61 exhibits similar binding to FcγRIIB and FcγRIIA within statistical error (see Exhibit C, Declaration of Dr. Scott Koenig, in particular paragraphs 5 and 6, and Exhibit 5). Accordingly, Budde does not disclose an antibody or fragment thereof comprising a variable domain that specifically binds to FcγRIIB with greater affinity than to FcγRIIA. Thus, like Weinrich, Budde does not anticipate any of independent claims 1, 23 and 89-90 or remaining claims 9-16, 30-32 and 108-109 as dependent therefrom.

The teachings of Bolland and Clynes do not offer any further evidence as to the inherent immunospecificity of II8D2 or KB61, specifically that either antibody is able to specifically bind to the extracellular domain of FcγRIIB endogenously expressed on the surface of a cell. In view of the foregoing, Applicants respectfully submit that the rejection under 35 U.S.C. § 102(a) as anticipated by Weinrich as evidenced by Bolland and Clynes has been obviated or overcome and should be withdrawn.

The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

The Rejection over Reff in view of Ott and Weinrich

The Examiner has rejected claims 1 and 17-21 under 35 U.S.C. § 103(a) as unpatentable over Reff et al., 2001, Crit. Rev. Oncol. Hematol. 40:25-35 ("Reff") in view of Ott et al., 2001, J. Allergy Clin. Imunol. 108:S95-S98 ("Ott") and Weinrich. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). Further, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981 (CCPA 1974).

Reff presents a general review of modifications to recombinant antibodies to increase their usefulness in the clinical setting. However, Reff provides no teachings or guidance as to an antibody comprising a variable domain that immunospecifically binds any FcγR, much less an antibody or fragment thereof comprising a variable domain that immunospecifically binds the extracellular domain of FcγRIIB with greater affinity than said *variable* domain binds FcγRIIA as recited in claim 1. Moreover, Reff provides no suggestion as to the manufacture or use of such an antibody. Thus, Reff does not render obvious the presently claimed invention.

Neither Ott nor Weinrich, alone or in combination, remedy the deficiencies of Reff. Ott is directed to a characterization of the mechanism by which FcγRIIB and its effector SHIP inhibit immune responses. Although Ott recognizes that FcγRIIB and/or SHIP may be effective therapeutic targets in the treatment of immunologic disorders, Ott provides no teachings or guidance as to a means of effectively targeting FcγRIIB, in particular, over FcγRIIA. Similarly, for the reasons discussed above, Weinrich does not disclose an antibody with such properties and, thus, does not teach or suggest a means of producing said antibody. The problem of producing an antibody with greater affinity for the extracellular domain of FcγRIIB over FcγRIIA had long been recognized in the art, which problem has been solved by the instant application. The Examiner's attention is respectfully invited to Exhibit D, a copy of Tam et al., 1995, Allergy

59:772-780, previously submitted as reference **C58** in the July 15 IDS ("Tam," published significantly after Ott and Weinrich) which evidences both the art recognized need for an antibody that immunospecifically binds the extracellular domain of FcγRIIB with greater affinity than that of FcγRIIA and the general skepticism that such an antibody could be developed (see Tam page 777, second full paragraph after "Discussion"). Thus, Ott and/or Weinrich, whether alone or in combination with Reff, do not render obvious the presently claimed methods. Accordingly, Applications submit that the rejection under 35 U.S.C. 103(a) over Reff in view of Ott and Weinrich has been obviated or overcome and should be withdrawn.

The Rejection over Presta in view of Ott and Weinrich

The Examiner has rejected claims 1 and 104-107 under 35 U.S.C. § 103(a) as unpatentable over Presta, U.S. Patent 6,737,056 ("Presta") in view of Ott and Weinrich. Applicants respectfully disagree with the Examiner for the reasons presented below.

Presta is directed to the modification of the Fc region of antibodies to alter binding of the *Fc* region to an FcγR. Presta does not teach or suggest antibodies with variable domains that immunospecifically bind to the extracellular domain of FcγRIIB with greater affinity than to FcγRIIA as recited in claim 1. Moreover, Presta teaches that the Fc region, and thus the modifications thereto, are not directly involved in antibody binding to an antigen via its variable domain (see Presta, *e.g.* Fig. 1, [0007]-[0008] and [0013]. Accordingly, Presta does not render obvious claim 1.

Neither Ott nor Weinrich, alone or in combination, remedy the deficiencies of Presta. For the reasons discussed above, neither Ott nor Weinrich teach or suggest the present invention; accordingly, Ott and Weinrich alone or in combination with Presta likewise do not render claim 1 obvious.

With respect to the rejection of claims 104-107, these claims are directed to antibodies comprising variable domains that immunospecifically bind to the extracellular domain of FcγRIIB with greater affinity than to FcγRIIA that also have a modification of their Fc region. As discussed above, because Presta, whether alone or in combination with Ott and Weinrich, fails to render obvious the antibody of claim 1, the combination of references likewise does not render obvious the antibody as recited in a claim dependent thereon, *e.g.*, the antibody as recited in any of claims 104-107. In this instance, the patentability of the claimed invention rests on the antibody that specifically binds FcγRIIB and modification of its Fc region would not render obvious an otherwise non-obvious antibody.

Accordingly, Applicants respectfully submit that the rejection of claims 1 and 104-107 under 35 U.S.C. § 103(a) over Presta in view of Ott and Weinrich has been obviated or overcome and should be withdrawn.

Provisional Rejection For Obviousness-Type Double Patenting

Claims 1, 9-21, 23, 30-32, 38, 41-43, 81-90, and 104-109 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 16-20 of U.S. Patent Application Serial No. 11/305,787 ("the '787 application") and claims 1-6, 9, 10, 14, 15, 53-57 and 63 of U.S. Patent Application Serial No. 11/108,135 ("the '135 application"). The Examiner contends that the claims are not patentably distinct from each other because claims 1-13 and 16-20 of the '787 application are drawn to the same or nearly the same anti FcγRIIB antibody that specifically binds the extracellular domain of human FcγRIIB and/or to an anti-FcγRIIB antibody with Fc modification; and because claims 1-6, 9, 10, 14, 15, 53-57 and 63 of the '135 application are drawn to the same or nearly the same anti-FcγRIIB antibody with identical clone name 2B6 that specifically binds the extracellular domain of human FcγRIIB and/or to an anti-FcγRIIB antibody with Fc modification.

In response, and without agreeing with the double patenting rejection, Applicants request that the obvious-type double patenting rejection be held in abeyance until indication of allowable subject matter.

The Rejection over U.S. Patent Application Serial Number 11/605,787

The Examiner has noted that claims 1, 9-21, 23, 30-32, 38, 41-43, 81-90, and 104-109 are drawn to invention not patentably distinct from claims 1-13 and 16-20 of U.S. Patent Application Serial No.: 11/305,787 and claims 1-6, 9, 10, 14, 15, 53-57, and 63 of U.S. Patent Application Serial No.: 11/108,135, and that these Applications would form the basis of a rejection under 35 U.S.C. § 103(a) if the commonly assigned cases qualified as prior art under 35 U.S.C. §§ 102 (e), (f) or (g) and were not commonly owned at the time the invention in the instant application was made.

Applicants respectfully submit that U.S. Patent Application Serial Nos. 11/305,787 and 11/108,135 are unavailable as prior art references under 35 U.S.C. § 103(a) pursuant to 35 U.S.C. § 103(c). In particular, at the time the invention claimed in the instant application was made, the subject matter of the instant claims and the subject matter of U.S. Patent Application Serial Nos. 11/305,787 and 11/108,135 were owned by, or subject to an obligation of assignment to, the same entity, that is MacroGenics, Inc.

Therefore, under 35 U.S.C. § 103(c), U.S. Patent Application Serial Nos. 11/305,787 and 11/108,135 are unavailable under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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